

WHAT IS CLAIMED IS:

1. A method of reducing the systemic release of radioactive decay intermediates upon administration of an alpha 5 particle-emitting radionuclide to an individual, comprising the steps of:

incorporating said radionuclide into large liposomes, said liposomes having a diameter sufficient to retain at least a majority of said radioactive decay intermediates; and

10 administering said large liposomes to said individual, wherein retention within said large liposomes of said radioactive decay intermediates produced by said radionuclide reduces the systemic release thereof.

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2. The method of claim 1, further comprising:

entrapping said radionuclide within smaller liposomal vesicles prior to incorporating said radionuclide contained therein into the aqueous phase of said larger liposome.

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3. The method of claim 2, further comprising:  
labeling said smaller liposomal vesicles with biotin.

5 4. The method of claim 1, further comprising the step  
of:  
coating outer membrane surfaces of said large liposomes  
with molecules which preferentially associate with a specific target  
cell thereby increasing specificity of said large liposomes to said  
10 target cell.

5. The method of claim 4, wherein said target cell is a  
cancer cell, a virally infected cell, an autoimmune cell, or an  
15 inflammatory cell.

6. The method of claim 4, wherein said molecules are  
antibodies, peptides, engineered molecules or fragments thereof.

7. The method of claim 6, wherein at least some of said antibodies are Herceptin.

5 8. The method of claim 1, further comprising the steps of:

preinjecting the individual with empty large liposomes;

and

10 saturating the reticuloendothelial organs to reduce non-tumor specific spleen and liver uptake of said radionuclide upon administration thereof.

9. The method of claim 1, wherein said large liposomes  
15 have a diameter of about 600 nm to about 1000 nm.

10. The method of claim 1, wherein said large liposomes comprise molecules incorporated into outer membranes to stabilize  
20 said large liposomes.

11. The method of claim 10, wherein said stabilizing molecules are polyethyleneglycol-linked lipids (PEG-lipids).

5 12. The method of claim 10, wherein said stabilizing molecules further comprise an antibody, peptide, engineered molecule or fragment thereof attached thereto.

10 13. The method of claim 1, wherein said large liposomes comprise a stabilizing agent incorporated therein or have an aqueous phase with a high pH thereby further facilitating retention of said radioactive decay intermediates.

15 14. The method of claim 13, wherein said stabilizing agent is a phosphate buffer, insoluble metal binding polymer, resin beads, metal-binding molecules or halogen binding molecules.

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15. The method of claim 1, wherein said large liposomes comprise additional molecules, said molecules facilitating membrane fusion with target cells or facilitating endocytosis by target cells.

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16. The method of claim 1, wherein said alpha particle emitting radionuclide is incorporated into the aqueous phase as a chelation compound.

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17. The method of claim 1, wherein said alpha-particle-emitting radionuclide is  $^{225}\text{Ac}$ ,  $^{223}\text{Ra}$ ,  $^{213}\text{Bi}$ , or  $^{211}\text{At}$ .

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18. The method of claim 1, wherein said alpha particle-emitting radionuclide is a daughter of a beta particle-emitting radionuclide, wherein said beta particle-emitting radionuclide is incorporated within said large liposomes.

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19. The method of claim 18, wherein said beta particle-emitting radionuclide is  $^{212}\text{Pb}$ .

5           20. A method of targeting cells in an individual for liposomal delivery of an alpha particle-emitting radionuclide thereto with reduced systemic release of radioactive decay intermediates comprising the steps of:

10           entrapping said radionuclide within small liposomal vesicles;

              incorporating said entrapped radionuclide into the aqueous phase of large liposomes, said liposomes having a diameter sufficient to retain at least a majority of the radioactive decay intermediates of said radionuclide, said liposome comprising:

15           polyethyleneglycol-linked lipids (PEG-lipids) on outer membranes thereof; and

              a targeting agent attached to the PEG-lipids, said targeting agent specific to the cells; and

20           delivering said radionuclide to the cells whereby said targeting agents target the cells while retention within said large

liposomes of said radioactive decay intermediates produced by said radionuclide reduces the systemic release thereof.

5           21. The method of claim 20, further comprising:  
labeling said smaller liposomal vesicles with biotin.

10          22. The method of claim 20, further comprising the  
steps of:

              preinjecting the individual with empty large liposomes;  
and  
              saturating the reticuloendothelial organs to reduce non-  
tumor specific spleen and liver uptake of said radionuclide upon  
15        delivery thereof.

20          23. The method of claim 20, wherein said large  
liposomes have a diameter of about 600 nm to about 1000 nm.

24. The method of claim 20, wherein said targeting agents are antibodies, peptides, engineered molecules or fragments thereof.

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25. The method of claim 24, wherein at least some of said antibodies are Herceptin.

10 26. The method of claim 20, wherein said targeted cells are cancer cells, virally infected cells, autoimmune cells, or inflammatory cells.

15 27. The method of claim 20, wherein said large liposomes further comprise a stabilizing agent incorporated therein or have an aqueous phase with a high pH thereby further facilitating retention of said radioactive decay intermediates.

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28. The method of claim 27, wherein said stabilizing agent is a phosphate buffer, insoluble metal binding polymer, resin beads, metal-binding molecules or halogen binding molecules.

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29. The method of claim 20, wherein said large liposomes further comprise additional molecules, said molecules facilitating membrane fusion with target cells or facilitating endocytosis by target cells.

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30. The method of claim 20, wherein said alpha particle emitting radionuclide is incorporated into the aqueous phase of said small liposomal vesicles as a chelation compound.

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31. The method of claim 20, wherein said alpha-particle-emitting radionuclide is  $^{225}\text{Ac}$ ,  $^{223}\text{Ra}$ ,  $^{213}\text{Bi}$ , or  $^{211}\text{At}$ .

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32. The method of claim 20, wherein said alpha particle-emitting radionuclide is a daughter of a beta particle-emitting radionuclide, wherein said beta particle-emitting radionuclide is entrapped within said small liposomal vesicles.

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33. The method of claim 32, wherein said beta particle-emitting radionuclide is  $^{212}\text{Pb}$ .

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34. A method of targeting cancer cells expressing HER-2/neu protein in an individual for liposomal delivery of Ac-225 thereto with reduced systemic release of radioactive decay intermediates thereof comprising the steps of:

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entrapping said Ac-225 within small liposomal vesicles; incorporating said entrapped Ac-225 into the aqueous phase of large liposomes, said liposomes having a diameter sufficient to retain at least a majority of the radioactive decay intermediates of Ac-225, said liposome comprising:

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polyethyleneglycol-linked lipids (PEG-lipids) incorporated into outer membranes thereof; and

Herceptin antibodies attached to the PEG-lipids; and  
delivering said Ac-225 to the cancer cells whereby said  
Herceptin targets the HER-2/neu protein expressed on the cells while  
retention within said large liposomes of said radioactive decay  
5 intermediates produced by said radionuclide reduces the systemic  
release thereof.

35. The method of claim 34, further comprising:  
10 labeling said smaller liposomal vesicles with biotin.

36. The method of claim 34, further comprising the  
steps of:  
15 preinjecting the individual with empty large liposomes;  
and  
saturating the reticuloendothelial organs to reduce non-  
tumor specific spleen and liver uptake of said radionuclide upon  
delivery thereof.

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37. The method of claim 34, wherein said large liposomes have a diameter of about 600 nm to about 1000 nm.

5 38. The method of claim 34, wherein said cancer cells comprise an ovarian carcinoma.

10 39. The method of claim 34, wherein said large liposomes further comprise a stabilizing agent incorporated therein or have an aqueous phase with a high pH thereby further facilitating retention of said radioactive decay intermediates.

15 40. The method of claim 39, wherein said stabilizing agent is a phosphate buffer, insoluble metal binding polymer, resin beads, metal-binding molecules or halogen binding molecules.

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41. The method of claim 34, wherein said large liposomes further comprise additional molecules, said molecules facilitating membrane fusion with target cells or facilitating endocytosis by target cells.

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42. The method of claim 34, wherein said Ac-225 is chelated.

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43. An encapsulated alpha particle emitting radionuclide, comprising:

    said alpha particle emitting radionuclide;

    small liposome vesicles entrapping said alpha particle

15    emitting radionuclide; and

    a large liposome incorporating said small liposome vesicles, said large liposome having a diameter sufficient to retain at least a majority of radioactive decay intermediates, said alpha particle emitting radionuclide thereby encapsulated therein.

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44. The encapsulated radionuclide of claim 43, further comprising:

labeling said smaller liposomal vesicles with biotin.

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45. The encapsulated radionuclide of claim 43, wherein said alpha particle emitting radionuclide is  $^{225}\text{Ac}$ ,  $^{223}\text{Ra}$ ,  $^{213}\text{Bi}$ ,  $^{212}\text{Pb}$ , or  $^{211}\text{At}$ .

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46. The encapsulated radionuclide of claim 39, wherein said alpha particle-emitting radionuclide is a daughter of a beta particle-emitting radionuclide, wherein said beta particle-emitting radionuclide is encapsulated.

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47. The The encapsulated radionuclide of claim 46, wherein said beta particle-emitting radionuclide is  $^{212}\text{Pb}$ .

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48. The encapsulated radionuclide of claim 43, wherein said radionuclide associates with a membrane of said small liposome or is incorporated into the aqueous compartment of said small liposome as a chelation compound.

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49. The method of claim 43, wherein said large liposomes have a diameter of about 600 nm to about 1000 nm.

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50. The encapsulated radionuclide of claim 43, wherein said large liposomes further comprise molecules which preferentially associate with a target cell, said molecules coating outer membrane surfaces of said large liposomes.

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51. The encapsulated radionuclide of claim 50, wherein said molecules are antibodies, peptides, engineered molecules or fragments thereof.

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52. The encapsulated radionuclide of claim 51, wherein  
at least some of said antibodies are Herceptin.

5 53. The encapsulated radionuclide of claim 50, wherein  
said target cell is a cancer cell, a virally infected cell, an autoimmune  
cell, or an inflammatory cell.

10 54. The encapsulated radionuclide of claim 43, wherein  
said large liposomes further comprise molecules incorporated into  
outer membranes to stabilize said large liposomes.

15 55. The method of claim 54, wherein said stabilizing  
molecules further comprise an antibody, peptide, engineered molecule  
or fragment thereof attached thereto.

56. The encapsulated radionuclide of claim 54, wherein said stabilizing molecules are polyethyleneglycol-linked lipids (PEG-lipids).

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57. The encapsulated radionuclide of claim 43, wherein said large liposomes comprise a stabilizing agent incorporated therein or have an aqueous phase with a high pH.

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58. The encapsulated radionuclide of claim 57, wherein said stabilizing agent is a phosphate buffer, insoluble metal binding polymer, resin beads, metal-binding molecules or halogen binding molecules.

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59. The encapsulated radionuclide of claim 43, wherein said large liposomes comprise molecules facilitating membrane fusion with a target cell or facilitating endocytosis by a target cell.

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